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Are antibiotics necessary in nonperforated appendicitis in children? A double blind randomized controlled trial

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SUMMARY

Background: *The use of antibiotics in uncomplicated appendicitis in children, remains the area of controversy. The aim of the study was to assess the necessity of antibiotic administration in nonperforated appendicitis in children.*

Material and methods: *The design of the study was a double blind randomized controlled trial, with a follow-up of 4 to 20 months. Setting: Surgical Department in a University Pediatric Hospital. Patients: One hundred and eighty seven out of 249 children subjected to emergency appendectomies met the inclusion criteria, with 35 eligible but not included in the study. The remaining 152 patients were randomized; 41 had complicated appendicitis, 3 other diagnosis, 108 were analyzed within 3 study groups: 1 (n=31) no antibiotic, 2 (n=41) one dose, 3 (n=36) 5-day course. Open appendectomy was a surgical procedure and Ceftriaxone 1.0 g i.v. was administered. Investigated parameters were: body temperature, WBC, bowel sounds, wound healing, recovery and morbidity.*

Results: *Valid outcome data were available for 90 of 108 randomized patients. Protocols of 18 children due to fever >39°C, upper airway infection or allergy were disclosed. In the remaining 90 children, there were no differences in WBC and oral feeding between groups 1 (n=24), 2 (n=35) and 3 (n=31). Group 1 and 2 had a higher mean temperature on day 1 post-op, without any clinical significance. A higher mean temperature was noted on day 5 post-op in group 1, due to wound infection in one patient. There were no intraabdominal abscesses. The only other complications were 2 adhesion small bowel obstructions (in groups 1 and 2 each).*

Conclusion: *Routine use of antibiotics in nonperforated appendicitis in children is not necessary.*

BACKGROUND

The major improvement in appendicitis outcome began with the antibiotic era. A mortality of 40% at the turn of the century was significantly diminished to 2.4% in the early 1940s [1]. With the advent of antibiotics, complications of appendectomy outnumbered mortality and further efforts were pursued in their reduction. Since then, however, relatively little progress has been made in lowering the overall morbidity [2]. Numerous papers published in the next decades dealt with new antibiotics, their combinations and route of administration. The wound infection rate of 45% [3] ceased to occur, after King et al. [4] announced the standard of using ampicillin, gentamicin and clindamycin in pediatric complicated appendicitis. Employing this protocol for a decade, Lund and Murphy achieved the lowest published wound infection rate of 3% in perforated appendicitis in children [5]. After the third-generation cephalosporins were introduced, this popular 'triple' regimen became obsolete [6]. Preoperative administration of antibiotics has proven to be effective in reducing the wound infection rate after potentially contaminated surgical procedures [7–9]. Controversy, however, persists in ap-

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pendectomies for nonperforated appendicitis, particularly in children. Some authors find prophylactic antibiotics effective in reducing septic complications after appendectomy for nonperforated appendicitis [10], others conclude that antibiotic prophylaxis in uncomplicated appendicitis, particularly in children, is highly questionable [11].

If it is assumed that:

– the inflamed appendix, without a perforation or peritoneal involvement, represents a resectable infection;
– children with acute appendicitis do not meet neither patient related nor perioperative and intraoperative criteria determined by factors of increased risk of postoperative infection;
– inappropriate use of prophylactic antibiotics may increase costs, side effects, and selection of resistant organisms [7];

we hypothesized, that routine antibiotic use in children with nonperforated appendicitis might be avoided.

MATERIAL AND METHODS

In order to verify this statement, we performed a prospective, double blind, randomized and placebo controlled clinical trial in children.

Patients' characteristics

The study protocol and consent form were approved by the institutional review board and research committee prior to the initiation of the trial. Informed consent was obtained from the parents or legal guardians of the children. The study was conducted in the surgical department of the 600-bed Jagiellonian University Children's Hospital in Krakow, Poland, between December 1993 and March 1995. During this time, 249 children were subjected to emergency appendectomies with the presumptive diagnosis of acute appendicitis. Their characteristics are presented in Table 1. Exclusion criteria from the study comprised: body weight less than 15 kg, allergy to penicillin or cephalosporin, antibiotic therapy within the previous 72 h or underlying illness requiring antibiotic therapy, evidence of diffuse peritonitis, or lack of written informed consent.

One hundred and eighty seven children were eligible for the study. One hundred and fifty two were successfully randomized. Those patients who were found intraoperatively to have a perforated appendicitis or intraabdominal abscess (n=41), or those misdiagnosed (n=3), were excluded from the protocol. The double blind study was conducted on 108 children.

Antibiotic

All patients were treated with the same agent. Due to the hospital pharmacy policy, identical but only two doses were prepared for the day and for the on call time. Ceftriaxone had been chosen. The wide range of the dosage (20–80 mg per kg of body weight), allowed the administration of 1.0 g to all children. Moreover, the drug could be administered once a day, witch was beneficial for the children in the placebo group. Antibiotics used for prophylaxis for postappendectomy infections should control E. coli and Bacteroides fragillis [8]. Ceftriaxone seems to meet these requirements [6,12].

Protocol: The patients were randomized into 3 study groups. The details of randomization were based on a table of random numbers and were unknown to anybody but the hospital pharmacy, which kept the master key and dispensed the drugs. The antibiotic and placebo were packed identically in opaque, numbered, ready for use i. v. bags. Each patient was administered intravenously the content of a bag every 24 hours for 5 days. The first dose was given 30–45 minutes before the skin incision. Group 1(n=31) received no antibiotic. Group 2 (n=41) received one preoperative dose. Group 3 (n=36) received a 5-day course started

Table 1. Patients' characteristics n = 249.

Eligible, subjected to study and randomized	**152**
Double blind study	108
Perforated appendix	41
Misdiagnosed (Meckel diverticulitis, omental torsion, intususception)	3
Eligible, not subjected to study	**35**
Hospital pharmacy limits	23
Negligence to administer	8
Physicians refusal(endocarditis prophylaxis, 2 handicapped children, family member)	4
Did not meet inclusion criteria	**62**
Lack of consent	30
Antibiotic < 72 h	23
Peritonitis	4
Body weight < 15 kg	3
Known allergy	2

preoperatively. At the time of manuscript preparation a 5-day antibiotic course after appendectomy was routinely employed in our department.

All operations were performed by the on duty team. To maintain uniformity in the operative procedure a standard protocol of open appendectomy was followed. The appendiceal stump was inverted. All specimens were sent to pathology, which established the final diagnosis. The peritoneum and the wound were irrigated with normal saline. No drains were inserted and the wound was closed primarily.

Study parameters

All patients were examined daily by the authors or by designated staff physicians and carefully assessed for the development of wound, intraabdominal or other infectious complications. For the purpose of this study wound infection was defined after Burnweit [13] as peri-incisional cellulitis or seropurulent wound drainage, whether culture positive or not. In addition to monitoring septic complications, body temperature was taken three times daily, WBC was counted daily and bowel sounds were examined with a stethoscope three times daily until they reappeared. Attention was also paid to possible side effects of the antibiotic.

If in any circumstance, observers or parents felt 'unsafe' with the effect of the masked drug, the protocol was disclosed. This situation occurred in 18 children out of 108 in whom the study had been started. Complete postoperative monitoring was performed in 90 children.

Upon discharge all patients were reevaluated at two weeks and one month after operation for the development of late complications. A questionnaire was also mailed 4 to 20 months after discharge to the parents in order to rule out possible late abdominal problems. The questionnaire was returned by 70% of the parents.

Statistical analysis

Chi-squared test was performed in the analysis of qualitative variables. The differences in quantitative variables within groups were identified using ANOVA and analyzed between groups by the Student's t-test. The normality of variables distribution was assessed with the Kolmogorov-Smirnov test. Significance was determined at $p<0.05$.

RESULTS

There were no significant differences in age, sex, body weight, WBC and temperature within groups 1–3 at admission.

The reasons for protocol disclosure are shown in Table 2. Table 3 presents the distribution of the children and pathology of the appendix in the 90 randomized children with valid outcome data.

The differences in appendix pathology within groups 1–3 were non-significant.

The side effects of ceftriaxone therapy were comprised of allergic reactions (rash) in 2 patients and colitis with massive Candida infection in 1 patient after a single dose in each case.

Table 2. Reasons for disclosure of 18 patients in the study.

	Group 1	Group 2	Group 3	Total
Fever	4	3	2	9
URTI*	2	1	2	5
Allergy	0	1	1	2
Candida colitis	0	1	0	1
Human error	1	0	0	1
Total	7¤	6¤	5¤	18
Study completed	24¤	35¤	31¤	90
Total	31	41	36	108

* Upper respiratory tract infection; ¤ Non-significant difference in the numbers of disclosed protocols in groups 1-3 (chi2 3x2 matrix)

Table 3. Distribution of randomized children and pathology of appendix.

	Normal	Simple acute	Phlegmonous	Gangrenous	Total
Group 1	2	2	15	5	24
Group 2	2	3	19	11	35
Group 3	2	1	16	12	31
Total	6¤	6	50	28	90¤

Non significant difference in pathology within groups 1-3 (chi^2 4x3 matrix)

Table 4. Observed differences of monitored variables of 90 children in groups 1-3.

Group	N	Temp.	WBC	Oral feeding	Wound infection	Other morbidity*
1	24	Yes	n.s.	n.s.	1 (4,2%)	1 (4,18%)
2	35	Yes	n.s.	n.s.	0	1 (2.7%)
3	31	n.s.	n.s.	n.s.	0	0

*Small bowel obstruction after 3 and 2 months postoperatively

The differences of monitored variables in groups 1–3 are shown in Table 4. Group 1 and 2 had a higher mean temperature on first postoperative day. A higher mean temperature was also noted on fifth postoperative day in group 1. Resolution of leucocytosis did not differ in groups 1–3. There was only one wound infection with Pseudomonas aeruginosa in a child from group one. This child was successfully treated with incision and drainage. No wound infection occurred in groups 2 or 3. The only other complications were two small bowel obstructions due to adhesions (in groups 1 and 2 each, occurred 3 and 2 months postoperatively).

DISCUSSION

Antibiotic prophylaxis in appendicitis, particularly in children, has been an area of controversy. A list of all known attempts for prevention of wound infection is very extensive and beyond the scope of this paper. Our clinical results of a randomized double blind study in 90 children were as follow: one wound infection in group one (4.2%); two small bowel obstructions due to adhesions (1 of 24 in group 1 and 1 of 35 in group 2, occurred beyond 30 post-op day) and temperature shifts in some measurements in group 1 and 2. The temperature average was higher on the first postoperative day in group 1 and 2, than in group 3. We did not find a clinical correlation to this phenomenon. The average temperature increase in group 1 on the fifth postoperative day was due to the wound infection in one patient. The wound exudate of this child cultured Pseudomonas aeruginosa. These bacteria were also isolated from peritoneum and appendix in this patient. Pseudomonas growth from the peritoneum may predict an infection even after antibiotic prophylaxis [14,15].

The wound infection rate of 4.2% without prophylaxis in our study seemed to be acceptable. In other placebo controlled trials, 'no antibiotic' wound infection rates ranged from 4% to 9% for simple appendicitis [7].

The reasons for opening the protocol of three out of 18 patients were the following side effects of the antibiotic therapy: two allergic reactions (rash) and one candida colitis.

The question remains whether all children with nonperforated appendicitis should be considered for routine prophylaxis. Prophylactic antibiotics are recommended when the risk of postoperative infection is high or in lower risk cases, when the consequence of the infection is extreme morbidity or mortality [7]. Postappendectomy wound infection in children does not constitute extreme morbidity. The most serious complication – intraabdominal abscess – did not occur in our study.

CONCLUSIONS

We suggest that routine use of antibiotics in nonperforated appendicitis in children is not necessary. The potential minimal reduction of the wound infection rate is counterbalanced by the side effects of antibiotics and the risk of emergence of resistant flora and opportunistic infections.

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